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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,427	07/17/2008	Masashi Isozaki	1029650-000178	2940

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
04/25/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/594,427	**Applicant(s)** ISOZAKI ET AL.	
	Examiner James D. (Doug) Schultz	**Art Unit** 1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 April 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *5* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-6,10-12 and 14-17*.
   Claim(s) withdrawn from consideration: *7-9,13 and 18*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/James D. (Doug) Schultz/
Primary Examiner, Art Unit 1633

Continuation of 3. NOTE: Claim 1 of the proposed claim amendment would incorporate limitations from claim 13, which has been withdrawn. Applicants present remarks argue that claim 13 should not be withdrawn since the limitations therein are alleged to relate to the manner in which the hydrophobic macromolecule is introduced. Supposing that applicants argument is correct, i.e. that claim 13 should not have been withdrawn for the reason above, entry of the proposed claim amendment would be denied since applicants proposed claim amendment narrows the scope of the claims by excluding a species that was previously embraced while prosecution was open (i.e. PEG-cholesterol derivatives). Since the art that was cited is directed against this embodiment, the rejection would have to be withdrawn, which would of course necessitate a new search in new considerations. Alternatively, if applicants argument is incorrect and claim 13 has been properly withdrawn, then entry of the proposed claim amendment would also be denied since the inclusion of previously withdrawn species would clearly require a new search and consideration. Accordingly, the proposed claim amendment will not be entered. Furthermore, applicants are reminded that there have been two different requirements/requests set forth on the record for applicants to furnish a list of claims that read on the elected invention (page 4, third line from the bottom of the restriction requirement of November 20, 2009, and page 2 bridging to page 3 of the nonfinal action of April 19, 2010). Applicants have declined to provide such a list on both occasions while prosecution was open, and it is not clear why the issue is being addressed for the first time now that prosecution has closed given the earlier opportunities. In the lack of evidence or reasoning to the contrary, the elected species PEG is considered to be distinct from PEG-phospholipid dirivatives, and the withdrawal of claim 13 is considered proper therefore.

Continuation of 11. does NOT place the application in condition for allowance because: Applicants argue that the rejection under 35 USC 103 lacks support for the elements necessary to make out a prima facie case of obviousness. Applicants argue that Harigai does not teach preparing liposomes containing drugs in the closed interior space of liposome, and that any implication by Harigai as to their liposomes' effectiveness as drug delivery vehicles is purely speculative. In response, it is set forth that one of ordinary skill in the art would readily understand that liposomes are well-known drug delivery agents, as acknowledged by applicants in the first two sentences of their specification ["Recently, a large number of investigations have been conducted on drug delivery system (DDS) for delivering and distributing a drug to the target lesion site at high efficiency with high safety. One such approach has been use of a closed vesicle such as liposome…"]. Furthermore, the first sentence of Harigai states that "Liposome formulations are currently being investigated as tools for the targeting delivery of drugs (1). Several liposomes, such as Doxil (2), have already been launched in the worldwide market. The surface of these liposomes has been modified with polyethylene glycol (PEG) to improve their stability in the blood (3)" Thus this fact is considered well known to those of ordinary skill in the art. As noted in the final rejection mailed November 5, 2010, Harigai concludes with the statement that their liposomes will become useful tools for development of drug targeting systems in the future. Accordingly, there is considered to be ample evidence that liposomes are well-known drug targeting compounds. this evidence exists throughout the prior art, and is furthermore corroborated in the background section of the instant specification. This argument is unconvincing therefore.

Applicants argue that Harigai never teach liposomes having a low the pH of the interior aqueous phase, and that the liposomes of Harigai contain saline at neutral pH. This is acknowledged in the rejection, which is not an anticipation rejection. Harigai was not relied upon for the teaching of a liposome possessing an acidic interior. Harigai was relied upon for teaching liposomes that comprise PEG on their outer surface, which Harigai not only exemplifies, but cites other prior art teaching the same thing. Put simply, PEG coated liposomes are not new. Harigai is missing only the acidic interior, which is taught by Mayer. Mayer teaches PEG modified cholesterol derivatives as part of liposomes possessing acidic interiors. The amount of overlap between these references is substantial. While applicants have attempted to amend around this teaching of Mayer, entry of this amendment has been denied as explained above and arguments directed to limitations not entered are not considered here. Applicants argue that Mayer only mentions PEG-cholesterol and does not provide an explanation that would lead toward the present invention. However, the Mayer reference is a US patent, which is not required to list that which is well-known to those of ordinary skill in the art. PEG-cholesterol derivatives are sufficiently well known that a full disclosure of PEG-cholesterol derivatives would not be required for patentability and would indeed add only to the length of their specification by disclosing that which is already well known in the art. Furthermore, being a US patent, the teachings of Mayer are considered to be enabled in the absence of evidence to the contrary, which applicants simply have not supplied.

Applicants allege that even if the teachings of Mayer and Harigai were combinable, the rejection does not provide any articulated reasoning with some rational underpinning to show why one would do so. Applicants also allege that there is no reason given in the rejection to explain why one would take the extra trouble to limit the hydrophobic hydrophilic macromolecule to the exterior surface of a drug-containing liposome preparation. However, it had been previously set forth that Harigai clearly envisions their liposomes as having drug delivery potential, and that the PEG elements of the liposomes of Harigai AND those of the prior art referenced in Harigai are explicitly described as existing on the exterior of their liposomes. Mayer does not explicitly state this, but does not need to state what one of ordinary skill in the art would know, which is that PEG is widely known in the art to be used for both targeting and immune evasion (for example, from the first paragraph of Harigai: "The surface of these liposomes has been modified with polyethylene glycol (PEG) to improve their stability in the blood (3), and as a result, better clinical results have been obtained through the modified liposomes' long circulation in the blood followed by the enhanced permeability and retention (EPR) effect (2)."). Thus the reasons for putting PEG on the exterior of a liposome are considered to be readily evident to one of ordinary skill in the art. In summary, Harigai teaches PEG coated liposomes that are disclosed as being useful in drug delivery, while Mayer teaches low pH liposomes conjugated PEG that one of ordinary skill in the art readily understands are useful almost exclusively when conjugated to the exterior of such liposomes. Arguments that the rejection does not provide any articulated reasoning with some rational underpinning are simply considered attorney arguments, which cannot take the place of evidence or reasoning. The rejection is maintained therefore.